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The Effects of Synthetic Cannabinoids on Alveolar-Arterial Oxygen Gradient

Sentetik Kannabinoidlerin Alveolo-Arteriyel Oksijen Gradienti Üzerine Etkileri

Synthetic Cannabinoids and Respiratory Functions

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Özet
Amaç: Sentetik kannabinoidler, insanlarda esrar benzeri bazı etkiler oluşturan kimyasallardır. Bu çalışmanın amacı, sentetik kannabinoidlerin alveolo-arteriyel oksijen gradienti üzerine etkilerinin araştırılmasıdır. Gereç ve Yöntem: Şubat 2014 ve Ağustos 2014 tarihleri arasında, sentetik kannabinoid kullanımı ile doğrudan acil servisimize başvuran toplam 112 hasta değerlendirildi. Kırk bir hastaya ait kan gazı örneği, oda havasında elde edilmiş arteriyel kan gazı olarak değerlendirilip çalışmaya dahil edildi. Hastalar, yaş, cinsiyet, dekat, parsiyel arteriyel oksijen basıncı, parsiyel arteriyel karbon dioksit basıncı, pH, bikarbonat, metabolik durum, yaşa göre beklenen alveolo-arteriyel oksijen gradienti ve hesaplanan alveolo-arteriyel oksijen gradienti değerlerine göre incelendi. Bulgular: Sentetik kannabinoid kullanımı erkeklerde fazla olup, ortalama yaş 23.32±6.14 idi. Üçüncü dekatta bulunan hasta sayısı, diğer dekatlara göre belirgin şekilde fazla idi. Hastaların hesaplanan alveolo-arteriyel oksijen gradienti, yaşa göre beklenen alveolo-arteriyel oksijen gradientine göre belirgin şekilde fazla idi. Solunumsal asidoz, metabolik bozukluğun diğer tiplerine göre belirgin şekilde fazla idi. Hesaplanan alveolo-arteriyel oksijen gradienti için en iyi kesim noktası 12.70 idi, bu noktada duyarlılık %90, özgüllük %85 olarak belirlendi. Hesaplanan alveolo-arteriyel oksijen gradienti için, eğri altında kalan alan 0.70 idi. Tartışma: Alveolo-arteriyel oksijen gradienti, sentetik kannabinoid kullanımına bağlı olarak yükselmektedir. Bu durum, sentetik kannabinoid kullanımının tanısında, destekleyici bir parametre olarak kullanılabilir.

Anahtar Kelimeler
Sentetik Kannabinoidler; Kan Gazları; Tanı

Abstract
Aim: Synthetic cannabinoids are chemicals that produce several marijuana-like effects in humans. Aim of this study is to investigate the effects of synthetic cannabinoids on to alveolar-arterial oxygen gradient. Material and Method: A total of 112 patients, who admitted directly to emergency clinic with synthetic cannabinoid usage, were determined between February 2014 and August 2014. Blood gases of 41 patients were determined as arterial blood gases on room air, and included in to study. Patients were evaluated according to age, sex, decade, partial pressure of arterial oxygen, partial pressure of arterial carbon dioxide, pH, bicarbonate, metabolic status, age consistent expected alveolar-arterial oxygen gradient and calculated alveolar-arterial oxygen gradient. Results: Synthetic cannabinoid using was higher in males, mean age of patients was 23.32±6.14 years. Number of patients in the third decade were significantly higher than the other decades. The calculated alveolar-arterial oxygen gradient value of patients was significantly higher than age consistent expected alveolar-arterial oxygen gradient value. Respiratory acidosis, was significantly higher than the other types of the metabolic disorders. The best cutoff point for calculated alveolar-arterial oxygen gradient was 12.70, with sensitivity of 90% and specifity of 85%. Area under curve was 0.70 for calculated alveolar-arterial oxygen gradient. Discussion: The value of alveolar-arterial oxygen gradient has been increased due to synthetic cannabinoid usage. This can be used as a supportive parameter in the diagnosis of synthetic cannabinoid usage.

Keywords
Synthetic Cannabinoids; Blood Gases; Diagnose

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Introduction

Synthetic cannabinoids (SC) are chemicals that produce several marijuana-like effects in humans. Synthetic cannabinoids are usually known as “Spice” in Europe, “K2” in United States of America and “Bonzai or Jamaika” in Turkey. These agents are obtained by spraying several different synthetic cannabinoids onto the vegetable ingredient, and herbal cigarettes mixtures that smoking in a similar way to cannabis by users [1]. Recently, SC usage has been increased, and more common seen in young adults and males [2]. Both animal studies and anecdotal clinical evidence suggest that the SC products may lead to more severe and unusual toxic effects than natural marijuana. The euphoric and psychoactive effects of SC are similar to marijuana, but SC have additional sympathomimetic symptoms, including diaphoresis, agitation, and restlessness [3]. The chemical structures of SC are similar to marijuana but there is no correlation between SC and Δ9-tetrahydrocannabinol in terms of toxicological investigations. Recognition of the signs and symptoms of intoxication and a high index of suspicion are necessary to diagnose SC toxicity [4]. In the literature there are several reports of rhabdomyolysis, kidney failure and acute myocardial infarction after SC usage. There have been a number of reports linking cannabis to pulmonary dysfunction. However, to date there are few reports that shows a link between SC and respiratory dysfunction [5-6].

Arterial blood gas analysis is a common investigation in emergency departments for monitoring patients with acute respiratory failure and considered the gold standard to determine oxygenation, patient’s gas exchange, ventilatory control and acid-base status in the acutely injured as well as critically ill patients. The impaired pulmonary function manifests in the form of decreased partial pressure of arterial oxygen (PaO2), an increased alveolar-arterial oxygen gradient (p(A-a)O2) [7].

The depressive respiratory effect of SC inhalation has not been thoroughly investigated in the medical literature. Aim of this study is to investigate the effects of SC usage on to alveolar-arterial oxygen gradient.

Material and Method

Patients who admitted directly to our emergency clinic for SC using, were determined from forensic records of hospital between February 2014 and August 2014. Due to unknown treatment and application form, patients who referred to our emergency clinic from another hospital were excluded from the study. A total of 112 patients were determined in this time period. Synthetic cannabinoid usage was confirmed by the patient or witnesses. Laboratory and clinical data were obtained from the digital medical records database of the hospital.

In this retrospective study, the effects of SC inhalation on alveolar-arterial oxygen gradient were determined by arterial blood gases of patients that not given oxygen therapy. For this purpose, measurements of arterial blood gases were obtained from the patients that room air, and non-incubated arterial blood gas measurements were evaluated. In 18 patients, blood gas samples were not taken during emergency department evaluation, these patients were excluded from study. Blood gas measurements of remaining 94 patients, were evaluated retrospectively with a chest disease specialist to confirm arterial blood gas samples on room air.

In some studies, relationship between arterial and venous blood gases has been investigated. In these studies, mean PaO2 value has been found between 55-115 mmHg, mean partial pressure of venous oxygen (PvO2) value between 25-48 mmHg, mean partial pressure arterial of carbon dioxide (PaCO2) value between 35-42 mmHg, mean partial pressure of venous carbon dioxide (PvCO2) value between 41-42 mmHg. Partial pressure of oxygen (PO2) is significantly different between arterial and venous blood gases according to partial pressure of carbon dioxide (PCO2). The saturation of oxygen (SO2) value has been found between 87-89 mmHg, in these studies [8-9-10]. According to these results, blood gases of 40 patients that PaO2 value less than 48 mmHg accepted as venous blood gases, and these patients were excluded from study. In 13 patients, value of SO2 was higher than 89 mmHg, these samples were accepted as arterial blood gases with oxygen treatment, and excluded from study. A total of 41 patients’ blood gas samples were determined as arterial blood gases on room air, and included to study. Patients were evaluated according to age, sex, decade, PaO2, PaCO2, pH, bicarbonate (HCO3), metabolic status, calculated p(A-a)O2 and age consistent expected p(A-a)O2. The p(A-a)O2 of patients was calculated according to formula of p(A-a) O2: [150-(1.25xPaCO2)]-PaO2. Age consistent expected p(A-a) O2 of patients was calculated according to formula of p(A-a) O2: 2.5+[0.25xage(years)] [11].

Data were analyzed using the Statistical Package for Social Sciences version 16.0. (SPSS: An IBM Company, version 16.0, IBM Corporation, and Armonk, New York, USA). All data were expressed as the mean ± standard deviation. The Student’s t test was used to compare the means for the studied variables. For comparing the continued two groups, Pearson Chi-square test was used. The P value smaller than 0.05 was considered statistically significant. The cut-off values of parameters for discrimination of the groups were determined using the Receiver Operating Characteristic (ROC) curve analysis. The areas under the ROC curves were calculated and the specificity, sensitivity and accuracy, for the parameters have been determined.

Results

A total of 112 patients were analyzed, 111 patients were male and only 1 patient was female. Synthetic cannabinoid using was significantly higher in males ($p < 0,001$), and mean age of patients was 23.32 ± 6.14 years (ranged: 15 to 48). Sixty two percent of patients were located between age of 18–24 years. There were 35 patients in the second decade, 60 patients in the third decade,15 patients in the fourth decade and only 2 patients in the fifth decade. Number of patients in third decade were significantly higher than the other decades ($p = 0,02$).

The mean arterial blood gas values of 41 patients that included in the study were shown in Table 1. The value of PaO2 was reduced according to reference range, but not statistically significant ($p > 0.05$). The value of PaCO2 was adjacent to upper limit of the reference range, but not statistically significant ($p > 0.05$). The value of calculated p(A-a)O2 was significantly higher than age consistent expected p(A-a)O2 value ($p = 0.02$). Respiratory acidosis was significantly higher than the other metabolic disorders ($p = 0.02$).

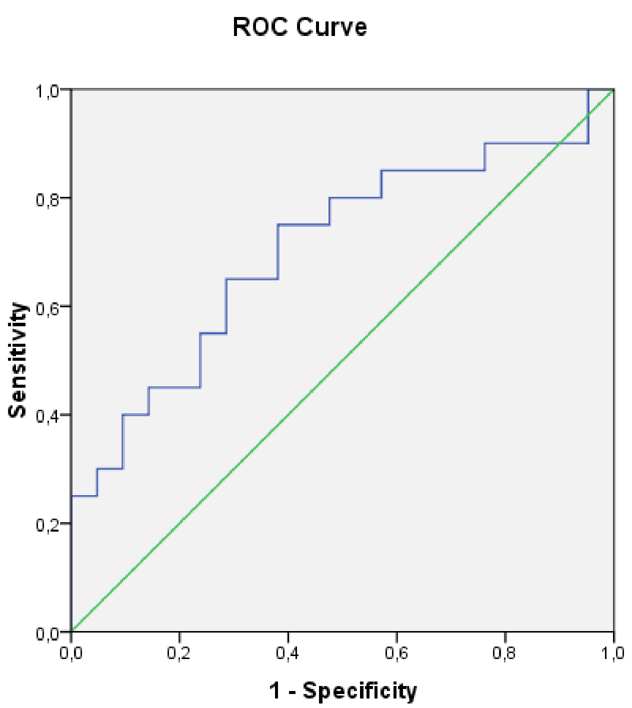
Table 1. Mean arterial blood gas values of patients.t

	Determined Value	Reference Range	p
PaO_2	63.95 ± 8.42 mmHg	(83-108 mmHg)	p > 0.05
$PaCO_2$	48.00 ± 6.93 mmHg	(35-48 mmHg)	p > 0.05
HCO_3	25.63 ± 2.59 mmHg	(22-26 mmol/L)	
pH	7.35 ± 0.04	(7.35-7.45)	
Age consistent expected p(A-a)O2	8.45 ± 1.74		
Calculated p(A-a)O2	26.02 ± 11.07	p = 0.02	
Metabolic Status			
Respiratory acidosis	20 patients	p = 0.02	
Normal values	9 patients		
Mixed respiratory acidosis + Metabolic alkalosis	8 patients		
Metabolic acidosis	2 patients		
Respiratory alkalosis	1 patient		
Compensated metabolic alkalosis	1 patient		

PaO_2; Partial pressure of arterial oxygen, $PaCO_2$; Partial pressure of arterial carbon dioxide, HCO_3; Bicarbonate, p(A-a)O_2; Alveolar-arterial oxygen gradient.

Receiver operating characteristic curve for calculated p(A-a)O2 was shown at Figure 1. Best cutoff point for calculated p(A-a) O2 was 12.70, with sensitivity of 90% and specifity of 85%. Area under curve was 0.70 for calculated p(A-a)O2.

Figure 1. Receiver operating characteristic curve for calculated alveolar arterial oxygen gradient.



Discussion

Synthetic cannabinoids are synthesized to mimic the action of Δ9- tetrahydrocannabinol, that is an active compound in marijuana [12]. Recently, SC usage and toxicity have been increased between young adults and males all across the world. Barratt and colleagues were found, mean age was 27 for SC use in Australia and 77% of users were male [13]. Hoyte and coworkers found, mean age for SC use was 22.5 and 74.3% of users were male [2]. Consistent with the literature, we found SC using was significantly higher in males and mean age of patients was 23.32 years. Most users are young adults, with the desire to experience cannabis-like effects with a substance that cannot be detected on routine drug tests. The relatively low cost is another reason for its popularity in the younger age group [14]. Although there is an extensive literature detailing respiratory effects of conventional cannabis marijuana and non-tobacco additives in cigarettes, pulmonary toxicity in the context of SC abuse is not as well-reported as toxicity in other organs. In some studies researchers indicated that, cannabis using was associated with higher lung volumes and increased large-airways resistance, but there was a little evidence for airflow obstruction or impairment of gas transfer in these studies [15-16]. In a study on conscious monkeys, SC agonists WIN55212-2 decreased tidal and minute volume, whereas respiratory frequency was not changed [17]. Tashkin sad that, Δ9-tetrahydrocannabinol in smoked marijuana initially relaxes airway smooth muscle and causes bronchodilation in both healthy persons and stable asthmatic patients, this bronchodilator effect is relatively short-lived (lasting as long as 60 minutes and six hours) and diminishes with the repeated use of marijuana (tachyphylaxis) [18]. Taylor et al. found a declined lung function in association with the development of chronic obstructive pulmonary disease (COPD) in chronic cannabis smokers [19]. Respiratory depression in rats receiving Δ9-tetrahydrocannabinol was reported in early publications but involvement of specific cannabinoid receptors could not be demonstrated [20]. Schmid and colleagues were showed that, increasing doses of the synthetic cannabinoid agonists WIN55212-2 and CP55940 markedly and dose-dependently lowered mean arterial pressure, heart rate and the plasma noradrenaline concentration in rats. These cardiovascular effects were accompanied by a large decrease in respiratory rate. CP55940, has been caused a decrease in PO2 and pH, whereas an increase in PCO2. The natural cannabinoid agonist, Δ9-tetrahydrocannabinol also decreased mean arterial pressure, heart rate, the plasma noradrenaline concentration and respiratory rate. The first major finding of this study was, cannabinoid agonists – both synthetic and natural – also elicit respiratory depression by acting at CB1 receptors, as shown by a marked decrease in respiratory rate, hypoxia, hypercapnia and arterial blood acidosis. Researchers speculated that cannabinoids could affect the function of different peripheral receptors involved in respiratory regulation. These agents could also influence airway resistance acting directly on the bronchi [21].
Like these studies, we found a higher level of PaCO2 and lower level of PaO2 according to reference range, but not statistically significant. And also, respiratory acidosis was the most common type of metabolic disturbance in our study. These findings may be a result of increased large-airways resistance, a large decrease in respiratory rate due to SC using and respiratory supressor effects of synthetic cannabinoids.
Additionally, we found significantly higher value of calculated p(A-a)O2 according to expected p(A-a)O2. The p(A-a)O2 is a simple way to measure alterations between the alveolus and capillary, and has recently been used in the study of different critical disorders such as COPD and pulmonary thromboembolism. The normal p(A-a)O2 increases with age. An abnormally

increased p(A-a)O2 suggests a defect in diffusion, ventilation/perfusion (V/Q) mismatch or right-to-left shunt [22].

The principal contributor to hypoxemia in COPD patients is V/Q mismatch resulting from progressive airflow limitation and emphysematous destruction of the pulmonary capillary bed [23]. The widening p(A-a)O2 was determined in some studies about COPD in the literature [24]. Like to COPD, cannabis usage was associated with higher lung volumes, suggesting hyperinflation and increased large-airways resistance [15-16]. Additionally, Taylor and Hall were sad that, a small but significant proportion of chronic cannabis smokers will exhibit decline in lung function in association with the development of COPD [19]. Due to similar nature of COPD and cannabis using, a significant higher level of calculated p(A-a)O2 in SC using can be explained by V/Q mismatch due to higher lung volumes, suggesting hyperinflation and intrapulmonary right-to-left microshunting due to lowered mean arterial pressure and heart rate.

Limitations

Synthetic cannabinoid using was not determined by the laboratory measurements in this study. And also we couldn't get simultaneous biochemical values. These are the most important limitations of this study. Due to retrospective nature of study, we do not know co-morbidities and how long the patients were using these agents. Additionally we do not know, if they use another agents such as cigarette.

Conclusion

Synthetic cannabinoid usage cannot be detected on routine drug tests, and has been increased between young adults and males. The calculated alveolar-arterial oxygen gradient is increased according to age consistent expected alveolar-arterial oxygen gradient in patients with synthetic cannabinoids usage. Increased alveolar-arterial oxygen gradient can be used as a supportive parameter in the diagnosis of synthetic cannabinoid usage.

Competing interests

The authors declare that they have no competing interests.

References

1. Evren C, Bozkurt M. Synthetic Cannabinoids: Crisis of The Decade. Düşünen Adam 2013;26(1):1-11.
2. Hoyte CO, Jacob J, Monte AA, Al-Jumaan M, Bronstein AC, Heard KJ. A characterization of synthetic cannabinoid exposures reported to the National Poison Data System in 2010. Ann Emerg Med 2012;60(4):435-8.
3. Cohen J, Morrison S, Greenberg J, Saidinejad M. Clinical Presentation of Intoxication Due to Synthetic Cannabinoids. Pediatrics 2012;129(4);1064-7.
4. Pierre JM. Cannabis, synthetic cannabinoids, and psychosis risk: What the evidence says. Curr Psychiatr 2011;10(9):49-58.
5. Jinwala FN, Gupta M. Synthetic cannabis and respiratory depression. J Child Adolesc Psychopharmacol 2012;22(6):459-62.
6. Alhadi S, Tiwari A, Vohra R, Gerona R, Acharya J, Bilello K. High times, low sats: Diffuse pulmonary infiltrates associated with chronic synthetic cannabinoid use. J Med Toxicol 2013;9(2):199-206.
7. Kiessling AH, Guo FW, Gökdemir Y, Thud M, Reyher C, Scherer M, et al. The influence of selective pulmonary perfusion on the inflammatory response and clinical outcome of patients with chronic obstructive pulmonary disease undergoing cardiopulmonary bypass. Interact Cardiovasc Thorac Surg 2014;18(6):732-9.
8. Byrne AL, Bennett M, Chatterji R, Symons R, Pace NL, Thomas PS. Peripheral venous and arterial blood gas analysis in adults: are they comparable? A systematic review and meta-analysis. Respirology 2014;19(2):168-75.
9. Razi E, Nasiri O, Akbari H, Razi A. Correlation of Arterial Blood Gas Measurements with Venous Blood Gas Values in Mechanically Ventilated Patients. Tanaffos 2012;11(4):30-5.
10. Bakoglu E, Kebapcioğlu AS, Ak A, Girisgin AS, Zararsiz I. Acil Serviste Periferik Venöz Kan Gazının Arter Kan Gazı Yerine Kullanılabilirliğinin Araştırılması. Eur J Basic Med Sci 2013;3(2):29-33.
11. Aygencel G. Arter kan gazlarının yorumlanması. Türk Kardiyol Dern Arş 2014;42(2):194-202.
12. Seely KA, Lapoint J, Moran JH, Fattore L. Spice drugs are more than harmless herbal blends: a review of the pharmacology and toxicology of synthetic cannabinoids. Prog Neuropsychopharmacol Biol Psychiatry 2012;39(2):234-43.
13. Barratt MJ, Cakic V, Lenton S. Patterns of synthetic cannabinoid use in Australia. Drug Alcohol Rev 2013;32(2):141-6.
14. Johnson LA, Johnson RL, Alfonzo C. Spice: A legal marijuana equivalent. Mil Med 2011;176(6):718-20.
15. Aldington S, Williams M, Nowitz M, Weatherall M, Pritchard A, McNaughton A, et al. Effects of cannabis on pulmonary structure, function and symptoms. Thorax 2007;62(12):1058-63.
16. Hancox RJ, Poulton R, Ely M, Welch D, Taylor DR, McLachlan CR, et al. Effects of cannabis on lung function: a population-based cohort study. Eur Respir J 2010;35(1):42-7.
17. Vivian JA, Kishioka S, Butelman ER, Broadbear J, Lee KO, Woods JH. Analgesic, respiratory and heart rate effects of cannabinoid and opioid agonists in Rhesus monkeys: antagonist effects of SR141716A. J Pharmacol Exp Ther 1998;286(2):697-703.
18. Tashkin DP, Shapiro BJ, Frank IM. Acute Pulmonary Physiologic Effects of Smoked Marijuana and Oral Δ9-Tetrahydrocannabinol in Healthy Young Men. N Engl J Med 1973;289(7):336-41.
19. Taylor DR, Hall W. Respiratory health effects of cannabis: Position Statement of The Thoracic Society of Australia and New Zealand. Intern Med J 2003;33(7):310-3.
20. Phillips RN, Turk RF, Forney RB. Acute toxicity of Δ9-tetrahydrocannabinol in rats and mice. Proc Soc Exp Biol Med 1971;136(1):260-3.
21. Schmid K, Niederhoffer N, Szabo B. Analysis of the respiratory effects of cannabinoids in rats. Naunyn-Schmiedebergs Arch Pharmacol 2003;368(4):301-8.
22. Casado MS, Díaz MQ, Palacios D, Hortigüela V, Schulke CM, García J, et al. Relationship between the alveolar-arterial oxygen gradient and PaO2/FiO2-Introducing peep into the model. Med Intensiva 2012;36(5):329-34.
23. Kent BD, Mitchell PD, McNicholas WT. Hypoxemia in patients with COPD: cause, effects, and disease progression. Int J Chron Obstruct Pulmon Dis 2011;6:199-208.
24. Dernaika TA, Beavin M, Kinasewitz GT. Iloprost Improves Gas Exchange and Exercise Tolerance in Patients with Pulmonary Hypertension and Chronic Obstructive Pulmonary Disease. Respiration 2010;79(5):377-82.

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